teaching a relational database containing cDNA sequencing data and correlations with previously known sequences. The Examiner takes the view that it would have been obvious to incorporate Zhao's predetermined sequence information into Seilhamer's database to allow the practitioner to input a query and rapidly access various data analysis. In rebuttal of applicants' previous arguments, the Examiner says that even if Zhao did not know sequence information beforehand, it would have been obvious for Zhao to display other information regarding sequences, such as a location identifier. Alternatively, the Examiner says that it would have been obvious to determine the sequences after performing the display for display at a later time.

This rejection is respectfully traversed. The Examiner's principal line of reasoning is based on the assumption that Zhao uses an array of cDNAs that have predetermined sequences. However, this is not the case. At p. 208, second column, second paragraph Zhao says that about 500 random cDNA were subject to single-run sequencing from the 3' end, and the sequences were compared with GenBank to determine which clones were present in multiple copies. The analysis revealed some sequence information for 406 clones and indicated that 181 of these were redundant (i.e., the same clone was present in more than one copy). The redundant clones were then used as hybridization probes to eliminate additional redundant clones from a primary repertoire of 5034 cDNA clones (p. 210, first column, first paragraph). 2756 clones that did not show hybridization to the redundant cDNA probes were then used in subsequent experiments. If these 2756 clones included the 406-181=225 unique clones subject to the initial single-pass sequencing, then some sequence information would have been known for 225 of the 2756 clones in Zhao's arrays. In fact, however, Zhao provides no indication that the 2756 clones used for hybridization experiments included the 225 clones for which some sequence information was available. If so, then sequence information was not available for any of the 2756 clones. In either event, the vast majority, if not all, of Zhao's clones were unsequenced when the hybridization experiment was performed. This is why Zhao performs sequence analysis of clones found to be of interest after the hybridization experiment (see Fig. 1 of Zhao). In the absence of sequence information for all, or almost all, of Zhao's clones, it seems highly implausible that one have have been motivated to combine Zhao's teaching with a reference discussing a sequence database and thereby reconfigure Zhao's computer program to display sequence information regarding clones in the manner proposed in the primary statement of the rejection.

The alternative scenario postulated by the Examiner in the event that Zhao does not disclose sequence information, namely, that it would have been obvious to modify Zhao to display a location identifier is purely conclusionary. The Examiner acknowledges that Zhao does

not teach displaying a plasmid location identifier of a displayed mark responsive to user input. The secondary reference does nothing to cure this deficiency. What remains is simply a conclusionary assertion that it would have been obvious to modify Zhao's method to include an element that the Examiner acknowledges is omitted. The only motivation asserted to support such a motivation is that of identifying a plasmid for further sequencing. However, Zhao must already had a scheme of correlating plasmid identity with expression data because without it he would not have been able to determine the identity of differentially expressed cDNA. The asserted motivation simply describes what Zhao was already doing. Nothing in Zhao or elsewhere indicates that any improvements in such a scheme were possible or desirable, much suggests the nature of such an improvement

The Federal Circuit has recently reemphasized that motivation must be specific and objective. *In re Dembiczak* 50 USPQ2d 1614 (Fed. Cir. 1999. *Dembiczak* concerned a simple invention to a trash bag with the appearance of a decorative pumpkin. The cited art was one reference describing a trash bag and another reference describing a paper bag with a pumpkin design. The Board below had combined the references based on their similarity to the invention and the fact that they collectively contained all the limitations of the claims. The Federal Circuit reversed because of lack of evidence of a specific motivation for combining the references. The Federal Circuit noted that the requirement for such evidence is particularly important when evaluating the patentability of inventions that can readily be understood, once described, as a safeguard against hindsight. The court held that such evidence must be "objective," and "clear and particular," and was not satisfied by "broad conclusory statements" (p. 1617).

Here, as in Dembiczak the presently claimed invention is of kind that is easily understood once described. With the benefit of hindsight provided by reading the present specification and seeing the ease with which the presently claimed method permit retrieval of information from marks representing expressed sequences, this modification of Zhao's method might indeed seem obvious. The question however is what would have motivated this improvement without the benefit of such hindsight and what was the specific evidentiary source of such motivation. Such a modification of Zhao is much easier to construct in hindsight with knowledge of the claimed invention than it would be prospectively. It is in precisely such circumstances that the requirement for evidence of particularized motivation is most acute as a safeguard against the "tempting but forbidden zone of hindsight." *Dembiczak at p. 1616.* In the absence of such a safeguard, the allegation of obviousness appears to be the result of hindsight.

The Examiner's final scenario in the event that Zhao's cDNAs were unsequenced prior to performing the hybridization is that one could determine the sequences of the cDNA's subsequent to displaying the type of plot shown in Zhao, perform correlations with Genbank and then go back and program Zhao's computer so that this information is displayed responsive to user imput in the manner claimed. However, this is not a plausible sequence of events based on the combined teaching of the two cited references. For example, suppose Zhao after performing his plot, selected several differentially expressed cDNAs for sequencing, and proceeded to determine the sequence of these clones. At this point, Zhao would already know the sequence and identity of each of his selected differentially expressed clones. Zhao could then input this information directly into Seilhamer's database to obtain further information characterizing the differentially expressed sequences. There would be in no purpose at this stage of the procedure in going back and reconfiguring Zhao's computer program to accept user input and display sequence information regarding selected marks corresponding to the sequenced cDNA's. The reconfigured program would simply display information that was already well know to the experimenter (i.e., the sequences of previously differentially expressed clones) or information that could be obtained more easily obtained simply by directly inputting the sequences of differentially expressed clones into Seilhamer's database.

Thus, the Examiner's proposed scenario involves an unexplained and unlikely departure from the expected conduct of a scientist attempting to practice the combined teachings of the cited references. Again, it appears that this departure results from a hindsight attempt to reconstruct the claimed invention based on the teachings of the specification, rather than motivation provided by the references.

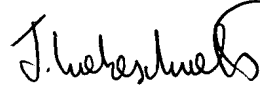For all of these reasons, withdrawal of the rejection is respectfully requested.

Claims 6-10 and 12-18 and 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al., WO97/27317 21, in view of Zhao et al., Gene Vol. 156, pp. 207-213, in further view of Seilhamer et al., U.S. 6,023,659. This rejection is traversed for at least the same reasons described above.

Claims 22, 24, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al., in view of Seilhamer et al., in further view Beattie, U.S. 5,843,767. This rejection is traversed for at least the same reasons described above.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al., in view of Seilhamer et al., in further view of Rosenberg et al., U.S. 6,028,593. This rejection is traversed for at least the same reasons as above.

If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 650-326-2400.

Respectfully submitted,

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